exponentially amplified. In contrast, the extension product of a signal primer is not available for further amplification. Accordingly - although a signal primer may be extended as claimed in step (b) of claims 21 and 29 - a signal primer extension product is not capable of exponential amplification. Signal primers extension products may be amplifiable in a linear fashion. See column 5, lines 3-14. Applicants believe it is this feature that allows the signal primers to be added to the amplification reaction mixture without promoting the high levels of background signal generated by other primer-based methods.

The signal primers of twice amended claims 21 and 29 do not result in the exponential amplification of their extension products. For example, in an SDA reaction, the signal primer extension product of the present invention may lack a nickable restriction endonuclease recognition site. For further example, amplification primers for NASBA, 3SR and TMA require an RNA polymerase promoter sequence in order to exponentially amplify. Accordingly, a signal primer according to the present invention in a NASBA, 3SR or TMA reaction may lack a promoter sequence for RNA polymerase. See Guatelli et al., "Isothermal, *in* vitro Amplification of Nucleic Acids by Multienzyme Reaction modeled after retroviral replication," *Proc. Natl. Acad. Sci.*, USA, Vol. 87: pp. 1874-1878, March 1990 (see Figure 1). See Hirose et al., "New Method to Measure Telomerase Activity by Transcription-mediated Amplification and Hybridization Protection Assay" *Clin. Chem.* 44:12, pp. 2446-2452 (1998). See Kievits et al., "NASBA™ Isothermal Enzymatic in vitro Nucleic Acid Amplification Optimized for the Diagnosis of HIV-1 Infection" *J. Virological Methods*, 35 (1991) pp. 273-286.

PCR does not require an additional sequence, such as a promoter sequence for RNA polymerase, in order for exponential amplification to occur. In PCR, any primer will function to create extension products that may be exponentially amplified. Accordingly, the method of twice amended claims 21 and 29 do not apply to PCR as disclosed in Mullis et al.

Thus, it is respectfully submitted that claims 21-42 are definite and withdrawal of the rejection is respectfully requested.

B. Enablement (35 U.S.C. § 112, 1st Paragraph)

The Examiner rejected claims 21-42, stating that "using the signal primer as claimed with any primer-based amplification is not predictable because the method steps of SDA reaction as disclosed in the specification are different from the method steps of the conventional primer based amplification as disclosed in the reference of Mullis et al. (4,965,188) ..."

However, as stated above, the method of twice amended claims 21 and 29 do not apply to PCR as disclosed in Mullis et al. because PCR does not require an additional sequence for exponential amplification. In contrast, amplification reactions such as SDA, NASBA, 3SR and TMA do require additional sequences for exponential amplification.

In determining whether the enablement requirement has been satisfied, factors to be considered include the state of the prior art and the relative skill of those in the art. In re Wands, 858 F2d 731, 737, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1988), *citing* Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Interf. 1986).

Methods for performing other amplification reactions such as NASBA, 3SR and TMA reactions were well known in the art. See Guatelli et al., "Isothermal, *in* vitro Amplification of Nucleic Acids by Multienzyme Reaction modeled after retroviral replication," *Proc. Natl. Acad. Sci.*, USA, Vol. 87: pp. 1874-1878, March 1990 (see Figure 1). See Hirose et al., "New Method to Measure Telomerase Activity by Transcription-mediated Amplification and Hybridization Protection Assay" *Clin. Chem.*, 44:12, pp. 2446/2452 (1998). See Kievits et al., "NASBA™ Isothermal Enzymatic in vitro Nucleic Acid Amplification Optimized for the Diagnosis of HIV-1 Infection" *J. Virological Methods*, 35 (1991) pp. 273-286.

As stated by the Examiner, "the level of skill in molecular biology is high." Accordingly, one of skill in the art knows how to carry out various primer-based amplifications and how to design a signal primer that lacks a sequence (such as a RNA polymerase promoter) and, thus, the ability to exponentially amplify. A person of ordinary skill would be not be subject to undue experimentation to practice claims 21-41.

Thus, it is respectfully submitted that claims 21-41 are fully enabled by the original specification and withdrawal of the rejection is respectfully requested.

C. Written Description (35 U.S.C. § 112, 1st Paragraph)

The Examiner rejected claims 21-41 alleging, "the recited element of the amended claims is not supported by the original disclosure." Applicants traverse.

The amendment language "wherein a characteristic of said signal primer is that it may not function as an amplification primer" is fully supported by the specification. Column 6, lines 26-43 states:

> "It is an important feature of the invention that the signal primers do not function as amplification primers in the SDA reaction in which they are employed. Without wishing to be bound by any specific mechanism by which the inventive methods work, Applicants believe it is this feature, which allows the signal primers to be added to the amplification reaction mixture without promoting the high levels of background signal generated by other primer-based methods. High levels of background signal are believed to be due to non-specific priming and subsequent amplification of spuriously primed non-target DNA when the primers are capable of functioning as amplification primers. The present invention therefore greatly simplifies the procedures for primer-based detection methods, which previously relied on two consecutive amplification reactions to attain high sensitivity and specificity, the second reaction being performed with internally nested signal-generating amplification primers."

Column 5, lines 10-14 states:

> "In contrast to amplification products, the double stranded secondary amplification product is generally not available for further amplification, although some secondary amplification products may be amplifiable in a linear fashion."

It should be noted that this language is generic and not limited to SDA.

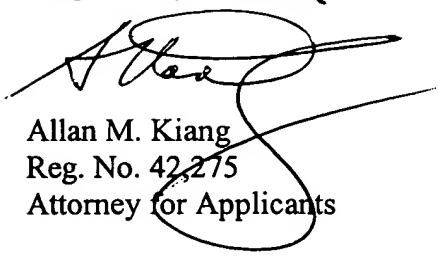
The Examiner also alleged "[t]here is no mention of PCR coupled amplification only SDA coupled amplification in the specification." Applicants traverse. As stated above, the method of twice amended claims 21 and 29 do not apply to PCR as disclosed in Mullis et al.

For the reasons stated above, it is respectfully submitted that twice amended claims 21-41 are supported by the disclosure. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSIONS

The claims of the present application are believed to be in condition for allowance. The Examiner is urged to telephone the undersigned regarding any further issues regarding this application.

Respectfully submitted,



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